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Antibody responses to influenza vaccination in patients with chronic renal failure

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Antibody responses to influenza vaccination in patients with chronic renal failure. A bivalent type A inactivated influenza virus vaccine containing both sets of H3N2 and $H_{sw_1}N1$ antigens was given to patients with chronic renal failure and to control subjects. The patients were divided into an azotemic group in whom dialysis was not yet required and a hemodialyzed group. Hemagglutination-inhibition (HI) antibody responses were measured at time intervals of 1, 3, and 4 weeks after vaccination. We found that the mean postvaccination HI titers against both sets of antigens in the patients as a group did not differ significantly from those found in the control subjects as a group. The proportion of responders showing a fourfold or greater increase in postvaccination antibody responses over prevaccination antibody values for either set of antigens was similar in both groups of patients and the group of control subjects. In general, an inverse correlation was found between prevaccination antibody levels and postvaccination antibody responses in both patients and control subjects. The only exception to this trend was the response of two of the azotemic patients to the H3N2 antigens who failed to respond despite low prevaccination antibody levels. These were the patients with the highest serum creatinine values.

Réponse immune à la vaccination anti-grippale chez les malades atteints d'insuffisance rénale chronique. Un vaccin antigrippal, bivalent, de type A, inactivé, contenant à la fois des antigènes H3N2 et $H_{sw_1}N1$ a été administré à des malades atteints d'insuffisance rénale chronique et à des témoins. Les malades ont été divisés en un groupe pour lequel l'hémodialyse n'était pas encore nécessaire et un groupe dialysé. L'hémagglutination-inhibition (HI) a été mesurée à des intervalles de temps de 1, 3, et 4 semaines après la vaccination. Dans l'ensemble nous avons constaté que les titres HI moyens postvaccinaux contre les deux types d'antigènes n'étaient pas significativement différents chez les malades par comparaison aux témoins. La proportion de réponses consistant en une augmentation de quatre fois ou plus du titre d'anticorps par comparaison avec les valeurs prévaccinales est similaire dans les deux groupes de malades et chez les contrôles. En général, une correlation inverse est trouvée entre les taux d'anticorps prévaccinaux et la réponse postvaccinale à la fois chez les malades et les contrôles. La seule exception à cette tendance est la réponse nulle de deux sujets azotémiques aux antigènes H3N2 malgré des taux d'anticorps prévaccinaux faibles. Il s'agissait des malades dont les créatinines plasmatiques étaient les plus élevées.

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Annual vaccination against influenza has been recommended for individuals with chronic illnesses [1, 2]. Before such a recommendation, however, can be extended to patients with chronic renal failure, it is important to know how well they respond to influenza vaccines. Jordan et al [3] found that maintenance hemodialysis patients responded adequately to inactivated influenza virus vaccines. In another study, Pabico et al found that azotemic nondialyzed patients had poorer antibody responses than did patients with nonazotemic renal disease [4]. To obtain more information on antibody responses to influenza antigens in patients with chronic renal failure, we compared hemagglutination-inhibition (HI) antibody responses to an inactivated bivalent influenza virus vaccine in nondialyzed azotemic patients, in patients treated with maintenance hemodialysis, and in healthy controls. The use of the inactivated bivalent vaccine containing A2/Victoria/1975 (H3N2) and A/New Jersey/1976 ($H_{sw_1}N1$) viruses enabled us to study antibody responses to a prevalent influenza virus (the former) and to study those responses to a less prevalent one (the latter, also known as swine flu virus).

Methods

Three groups of individuals took part in this study, which was performed between December 1976 and January 1977. During that period, epidemic influenza was not encountered in our community. None of the participating individuals received corti-

costeroid or immunosuppressive drugs for at least 12 months before investigation.

Control group. The control group consisted of 17 males, 40 to 63 years of age (mean age, 50.4), and 7 females, 42 to 53 years of age (mean age, 47.4). They were hospital personnel who had normal renal function as ascertained by normal urinalysis and serum urea nitrogen and creatinine levels.

Azotemic patients. The azotemic-patient-group consisted of 10 males, 33 to 65 years of age (mean age, 53.1). Their mean serum urea nitrogen was 34 mg/dl (range, 25 to 80), and their mean serum creatinine measured 3.9 mg/dl (range, 1.9 to 8.3). Renal failure was secondary to nephrosclerosis in 6 patients, chronic glomerulonephritis in 2, polycystic kidney disease in 1, and diabetic nephropathy in 1. All of these patients were clinically stable and did not require dialytic therapy.

Hemodialyzed patients. The patient-group on maintenance hemodialysis consisted of 19 men, 37 to 72 years of age (mean age, 53.5). Duration of hemodialysis treatments varied from 1 week to 9 years and 2 months (mean, 35.6 months). Renal failure was caused by nephrosclerosis in 8 patients, chronic glomerulonephritis in 4, polycystic kidney disease in 3, chronic interstitial nephritis in 3, and diabetic nephropathy in 1.

Study plan. Each subject received i.m. 0.5 ml of a bivalent influenza virus vaccine containing 400 chicken cell agglutinin (CCA) units. Half was in the form of A2/Victoria/1975 virus (H3N2 antigens), and the other half, A/New Jersey/1976 virus ($H_{sw_1}N1$ antigens). The vaccine (produced by Parke-Davis Co.) was that distributed by National Influenza Vaccination Program of 1976. No adverse reactions to the vaccine were encountered.

Sera samples were collected from the subjects before vaccination and at intervals of 1, 3, and 4 weeks after vaccination. We were unable to obtain a complete set of serum specimens from two azotemic and two hemodialyzed patients. Serum samples were stored at −20° C. Prior to analysis, each sample was treated with a standard receptor-destroying enzyme (Microbiological Associates) to inactivate any nonspecific inhibitors of hemagglutination [5]. Subsequently, it was tested for specific hemagglutination-inhibition activity against commercially prepared A2/Aichi 2/1968 virus possessing H3N2 antigens and A/New Jersey/1976 virus possessing $H_{sw_1}N1$ antigens. The former virus is a prototype of A2/Victoria/1975 virus. Sera samples were tested at an initial dilution of 1 : 8 or higher.

Prevaccination antibody levels were expressed as geometric mean hemagglutination-inhibition titers in the form of $\log_2$ HI titer ± standard error of the logarithm of the mean. In addition, postvaccination antibody responses were expressed as multiples of the initial prevaccination antibody levels in the form of $\log_2$ x. For example, a fourfold postvaccination antibody response is expressed as 2.0. The data were evaluated by analysis of variance, correlation between two variables, χ^2, and Student's t test.

Results

Antibody titers. The influenza antibody status of our study population prior to vaccination is in agreement with that reported previously for people over 30 years of age [6]. The majority of the study population had preexisting antibodies to the H3N2 and $H_{sw_1}N1$ antigens. Preexisting antibodies to the H3N2 antigens were not observed in one azotemic and one hemodialyzed patients. In addition, preexisting antibodies to the $H_{sw_1}N1$ antigens were absent in five control, one azotemic, and one hemodialyzed subjects.

Prevaccination antibody levels against the H3N2 antigens were significantly higher than were those against $H_{sw_1}N1$ antigens in control ($t = 6.22$, $P < 0.01$) and hemodialyzed subjects ($t = 3.56$ $P < 0.01$). In the nondialyzed azotemic patients, however, prevaccination antibody titers against the two sets of antigens were not statistically different ($t = 1.0$, $P = 0.0$) (Table 1). In each group of subjects, postvaccination antibody responses against either sets of antigens obtained at intervals of 1, 3, and 4 weeks after vaccination showed significant increases when compared to prevaccination values. Moreover, the three groups had similar postvaccination antibody responses at each interval. Finally, in the control group antibody titers of the women were similar to those of the men.

Responses to the two sets of antigens in the vaccine. After vaccination, 55% of the study population generated a fourfold or greater increase in HI titer to the H3N2 antigens, whereas 90% showed a comparable increase to the $H_{sw_1}N1$ antigens (Table 2). The proportion of responders showing such an increase in titer was similar among the groups. In addition, within each group, the geometric mean of postvaccination increments in titers to the $H_{sw_1}N1$ antigens was greater than was that to the H3N2 antigens (Table 2).

In general, intensity of antibody response of our subjects to the two sets of antigens was observed to be inversely related to their prevaccination antibody levels (Table 2). The sole exception was the

Table 1. Hemagglutination-inhibition (HI) titers following vaccination with inactivated influenza virus vaccine in patients with chronic renal failure and in control individuals[a]

Viral antigens	Groups	Serum HI titers[b]				
			Postvaccination			
		Prevaccination	1 week	3 weeks	4 weeks	P^c
H3N2	Azotemic	5.4 ± 0.54 (10)	6.3 ± 0.65 (10)	8.0 ± 0.93 (8)	8.0 ± 0.74 (8)	< 0.05
	Hemodialyzed	6.4 ± 0.34 (19)	6.5 ± 0.32 (18)	7.9 ± 0.47 (17)	7.7 ± 0.43 (18)	< 0.05
	Control	6.0 ± 0.22 (24)	7.4 ± 0.43 (24)	7.7 ± 0.26 (24)	8.0 ± 0.46 (24)	< 0.01
$H_{sw_1}N1$	Azotemic	4.7 ± 0.29 (10)	6.0 ± 0.37 (10)	7.6 ± 0.46 (8)	7.9 ± 0.40 (8)	< 0.01
	Hemodialyzed	5.0 ± 0.31 (19)	5.8 ± 0.38 (18)	7.9 ± 0.30 (17)	7.9 ± 0.33 (18)	< 0.01
	Control	4.0 ± 0.31 (24)	5.9 ± 0.43 (24)	7.1 ± 0.34 (24)	7.5 ± 0.31 (24)	< 0.01

[a] Number of subjects are denoted in parentheses.
[b] Geometric mean HI titers are expressed as $\log_2$ HI titers ± standard errors of the logarithms of the means.
[c] Comparisons were among HI titers obtained prevaccination and at time intervals of 1, 3, and 4 weeks, respectively, after vaccination, by a one-way analysis of variance.

Table 2. Antibody response to vaccination with inactivated influenza vaccine in patients with chronic renal failure and in control individuals

Viral antigens	Groups	Proportions of subjects showing 4-fold or greater increase in HI titers	Geometric means of increments in HI titers above prevaccination levels[a]	Correlation coefficients between prevaccination antibody levels and postvaccination antibody responses	*P*
H3N2	Azotemic	6/10 (60%)	2.4 ± 0.56	+0.1163	>0.05
	Hemodialyzed	10/19 (53%)	1.6 ± 0.37	−0.4654	<0.05
	Control	13/24 (54%)	2.0 ± 0.32	−0.6255	<0.01
	Total	29/53 (55%)			
$H_{sw_1}N1$	Azotemic	9/10 (90%)	3.2 ± 0.44	−0.7236	<0.01
	Hemodialized	17/19 (89%)	3.2 ± 0.24	−0.4805	<0.05
	Control	22/24 (92%)	3.7 ± 0.33	−0.5418	<0.01
	Total	48/53 (90%)			

[a] Geometric means of fold-increases in titers above prevaccination levels are expressed as $\log_2 x$; that is, a difference between prevaccination titer and postvaccination response of 2.0 is equivalent to a fourfold increase.

response of the azotemic patients to the H3N2 antigens. In these, there was no statistical relationship between prevaccination antibody levels and postvaccination antibody responses. Finally, in the hemodialyzed group, we found no correlation between postvaccination antibody responses and duration of dialysis.

Effect of azotemia on antibody responses. To determine whether severity of azotemia impaired antibody production, we examined the correlations among serum creatinine values, prevaccination antibody levels, and postvaccination antibody responses in the azotemic patients (Table 3 and Fig. 1). With regard to antibody production against the H3N2 antigens, statistical analysis demonstrated negative correlations between serum creatinine values and prevaccination antibody levels, as well as between serum creatinine and postvaccination antibody responses. It should be noted, however, that the significance of these correlations is uncertain since there were only two patients with serum creatinine values above 5 mg/dl, and both of these failed to generate a fourfold antibody response to the H3N2 antigens despite low prevaccination titers. Moreover, two additional patients with a blunted response had serum creatinines below 5 mg/dl, but these had the highest prevaccination antibody titers, which may have blunted the postvaccination response independently of the azotemic state [6]. In any case, azotemia did not adversely affect the antibody response to $H_{sw_1}N1$ antigens.

Table 3. Correlations among serum creatinine value, prevaccination antibody level, and postvaccination antibody response in azotemic patients

Variables	Correlation coefficients	
	H3N2	$H_{sw_1}N1$
Serum creatinine and prevaccination antibody level	−0.6082[a]	−0.1069
Serum creatinine and postvaccination antibody response	−0.6382[a]	+0.1042

[a] Significant at $P < 0.05$.

Discussion

This study demonstrates that mean postvaccination antibody responses of azotemic and hemodialyzed patients following injection of an influenza virus vaccine (H3N2 and $H_{sw_1}N1$ antigens) were comparable to those of individuals with normal renal function. Our findings in hemodialyzed patients confirm those of Jordan et al [3], who showed that when given a bivalent, type A and B influenza virus vaccine, hemodialyzed patients were able to produce serum HI antibody responses similar to those of healthy subjects.

Although our azotemic patients as a whole produced antibodies against the two sets of influenza antigens in a manner grossly similar to that of control subjects, our data, taken together with those of Pabico et al [4], suggest that advanced azotemia may selectively depress antibody responses to the H3N2 antigens. In our two patients with the highest serum creatinines, postvaccination antibody response to the H3N2 antigens was markedly suppressed (Fig. 1). Pabico et al [4] found that of their seven azotemic patients with serum creatinines ranging from 2.3 to 14.1 mg/dl, only one showed a fourfold or greater postvaccination antibody response against the H3N2 antigens. Note that all except two of their patients had serum creatinines above 5 mg/dl. Some of Pabico's patients, however, were on corticosteroids or immunosuppressive drugs, or both, and a different method of antibody determination was used.

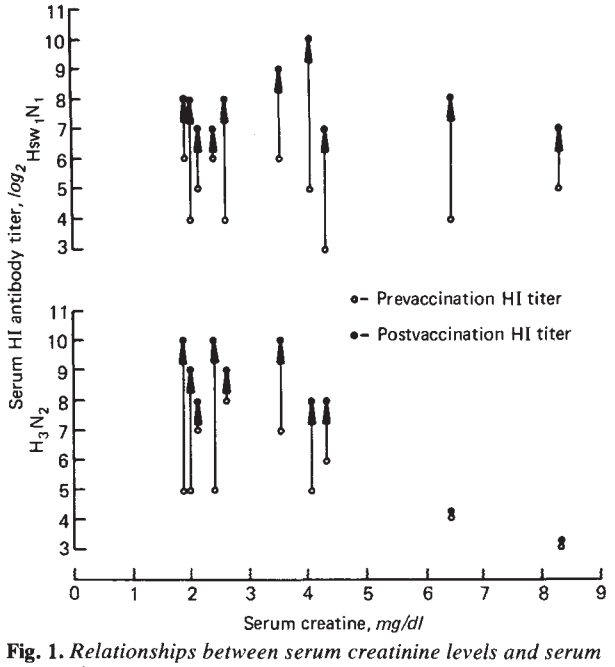

Fig. 1. *Relationships between serum creatinine levels and serum hemagglutination-inhibition (HI) antibody titers (both prevaccination and postvaccination) in azotemic patients.* For the H3N2 antigens, significant negative correlations were demonstrated between serum creatinine and prevaccination antibody titers, as well as between serum creatinine and postvaccination antibody responses. In the case of $H_{sw_1}N1$ antigens, no similar correlations were found.

Other studies on the effect of azotemia on antibody response to influenza vaccination in renal allograft recipients have yielded conflicting results. For example, Pabico et al observed that renal transplant recipients having creatinine clearances of 70 ml/min or higher had a better response to influenza vaccination than did those with lower creatinine clearances [7]. Other investigators, however, were unable to detect any relationship between antibody response and the severity of azotemia in similar patients [8, 9]. It is apparent that more studies are needed in patients with advanced azotemia to clarify the potential role of this state on the immunonogenicity of the several influenza antigens.

Split-influenza virus vaccines, as used in the present study, are reportedly less effective than whole virus vaccines in eliciting antibodies in persons who have not previously encountered the antigens in the vaccines. Studies conducted by NIAID [6], however, demonstrated that in persons possessing antibodies to influenza virus antigens prior to vaccination, both the split and whole virus vaccines are potent in inducing antibody formation.

The number of patients used in the present study was too small for evaluation of the protective effects of the vaccine. The mean HI titers reached by our patients, however, are comparable to those found to be protective by others [6]. With the exceptions noted above, our data suggest that both azotemic and hemodialyzed patients do have the ability to generate adequate antibody responses to influenza vaccination.

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